Definition of the Clinical Antibacterial Spectrum of Activity

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INTRODUCTION

The concept of clinical antibacterial spectrum of activity has been developed in order to make the summary of product characteristics (SPC) as helpful as possible to the clinician faced with prescribing an antibiotic empirically. The SPC is an official document established at the time of approval for marketing (AMM) and delivered by the French Ministry of Health: it must necessarily be shown on all documents related to this antibiotic. It includes especially the clinical indications based on the clinical antibacterial spectrum, the pharmacokinetics of the product, and the possible side effects.

Every antibiotic is characterized by a natural spectrum of antimicrobial activity that has been precisely determined during the initial phases of its study, long before it is introduced into clinical practice. This spectrum of activity, which includes the strains that can be inhibited by the antibiotic, does not vary qualitatively, although the percentages of susceptible bacterial strains in a species may change over time with the development of resistance. For example, penicillin G and vancomycin both include *Staphylococcus aureus* in their spectrum of activity. However, whereas the number of strains susceptible to penicillin G is currently less than 10%, it is still 100% for vancomycin.

In the absence or before results of susceptibility tests are available, the clinician must select an antibiotic which not only includes in its spectrum of activity the species most likely responsible for the infection but also statistically presents a reasonable chance of being active against the particular strain. It is obvious that this requirement is more stringent in more severe infections. For example, to treat meningitis it is an obligation to use the more likely active antibiotics, with the lowest risk of resistant strains [1].

DETERMINATION OF THE NATURAL SPECTRUM OF ACTIVITY OF AN ANTIBIOTIC

This represents the first step in the study of an antibiotic. Every antibiotic has to be investigated against several hundreds of strains belonging to species pathogenic for humans. The strains should be representative of all of these species, and each species should include strains of various origins susceptible or possessing definite mechanisms of resistance. The study of a large number of strains per species allows the determination of the modal minimal inhibitory concentration (MIC) of the susceptible population. This value characterizes the bacterium–antibiotic pair and allows comparisons of activities of different antibiotics. Strains possessing a particular mechanism of resistance must also be studied. Their modal MICs correlated to the pharmacokinetic data delineate some of the questions which should be answered by the clinical trials.

Strains that are not included in the natural spectrum of activity of an antibiotic are referred to as being naturally resistant to this antibiotic. Some natural resistance characteristics are of important taxonomic value (e.g. polymyxin and *Serratia*).

CLINICAL CATEGORIZATION

The clinical categorization is based on the study of the MIC distribution against bacterial populations within a representative sample of strains, detection of mechan-

isms of resistance and comparison with clinical and pharmacokinetic data [2–7]. These results in the determination of two critical concentration breakpoints, high and low (Figure 2), separating the three clinical categories enable the clinician to anticipate the effect of antibiotic therapy.

- Susceptible strain: the probability of therapeutic response is very high.
- Resistant strain: the risk of non-response to treatment is high.
- Intermediate strain: the therapeutic outcome is unpredictable. This category is heterogeneous because it combines a buffer zone due to biological methods, a zone of uncertainty due to variation in clinical response, and lastly particular cases where a bacterial strain could be targeted when local antibiotic concentrations are high (urine).

CLINICAL SPECTRUM OF AN ANTIBIOTIC (Table 1)

The clinical spectrum of an antibiotic is a formulation which is based upon the ability of the antibiotic to cure infections due to the designated bacteria [8]. Thus, bacterial species are included only when clinical efficacy was demonstrated and relevant for the approved indications. For example, *Legionella* spp. should be included in the clinical spectra of macrolides, fluoroquinolones and rifampicin but not in those of aminoglycosides or β-lactams, despite their in vitro activity. Certain species are not included in the spectrum of activity: these are species which cause local infections in sites where the antibiotic does not diffuse in sufficient concentrations even though it is active in vitro (e.g. *Neisseria meningitidis* and first-generation cephalosporins or macrolides). This also involves species which cause infections for which the antibiotic has not been approved for certain therapeutic indications by the marketing authorization submission, since the demonstration of therapeutic efficacy in these cases has not been provided.

The clinical spectrum of activity of an antibiotic takes the following items into account [4–6]:

- natural spectrum of activity
- modal MICs of susceptible strains
- pharmacokinetic data
- clinical results

Ideally, the clinical spectrum of an antibiotic should include the necessary information on the epidemiology of resistant strains. This important information is, however, difficult to include without some generalization.

Table 1 Clinical spectrum of activity of erythromycin

Usually susceptible species (MIC ≤1 mg/L)
Streptococcus pyogenes
Modal MIC = 0.03 mg/L
Frequency of acquired resistance: <10% in France
Excellent clinical activity (sore throats)
Moderately susceptible species (MIC 2–4 mg/L)
Haemophilus influenzae
Modal MIC = 4 mg/L for 60% of strains (very low level natural resistance)
No acquired resistance
Clinical results vary depending on the antibiotic concentrations in the body
Resistant strains (MIC > 4 mg/L)
Escherichia coli
Modal MIC = 32–64 mg/L
Natural resistance is incompatible with therapy
Methicillin-resistant *Staphylococcus aureus*
Frequency of acquired resistance: approximately 95% of strains
MIC >64 mg/L
Inconstantly susceptible species
Streptococcus pneumoniae
Modal MIC for susceptible strains = 0.03 mg/L
Frequency of acquired resistance: 30–40%

Bacterial resistance to antibiotics evolves in a highly variable way depending on the time and the places (ward in a hospital section in a city, region, etc.).

In some cases after a period of time, the prevalence rates of resistant strains stabilize and even become comparable in different geographic areas (e.g. *Staphylococcus* and *Haemophilus influenzae* producing penicillinase).

In other situations, the resistance rate will vary considerably from one country to another; for example, resistance to macrolides in *Streptococcus pneumoniae* is high in France (30–40%) and still low in the USA (<5%) [9]. Undue applications of foreign epidemiologic data in a country may have serious consequences.

To prescribe an antibiotic with the maximum chance of clinical response, the physician should know the status of resistance of the major species of bacteria in the location where he or she is practicing. This requires, up to date epidemiologic data on resistance and the analysis of clinical failures with accurate bacteriologic documentation.

To recognize the resistant strains in a population of strains, the MIC 50% and the MIC 90% are of limited value, since the interval between MIC 50% and MIC 90% is the only indication of possible resistant populations. We think that the histogram of the strains tested is more informative than the cumulative percentage, since it shows the distribution and the number of subpopulations.

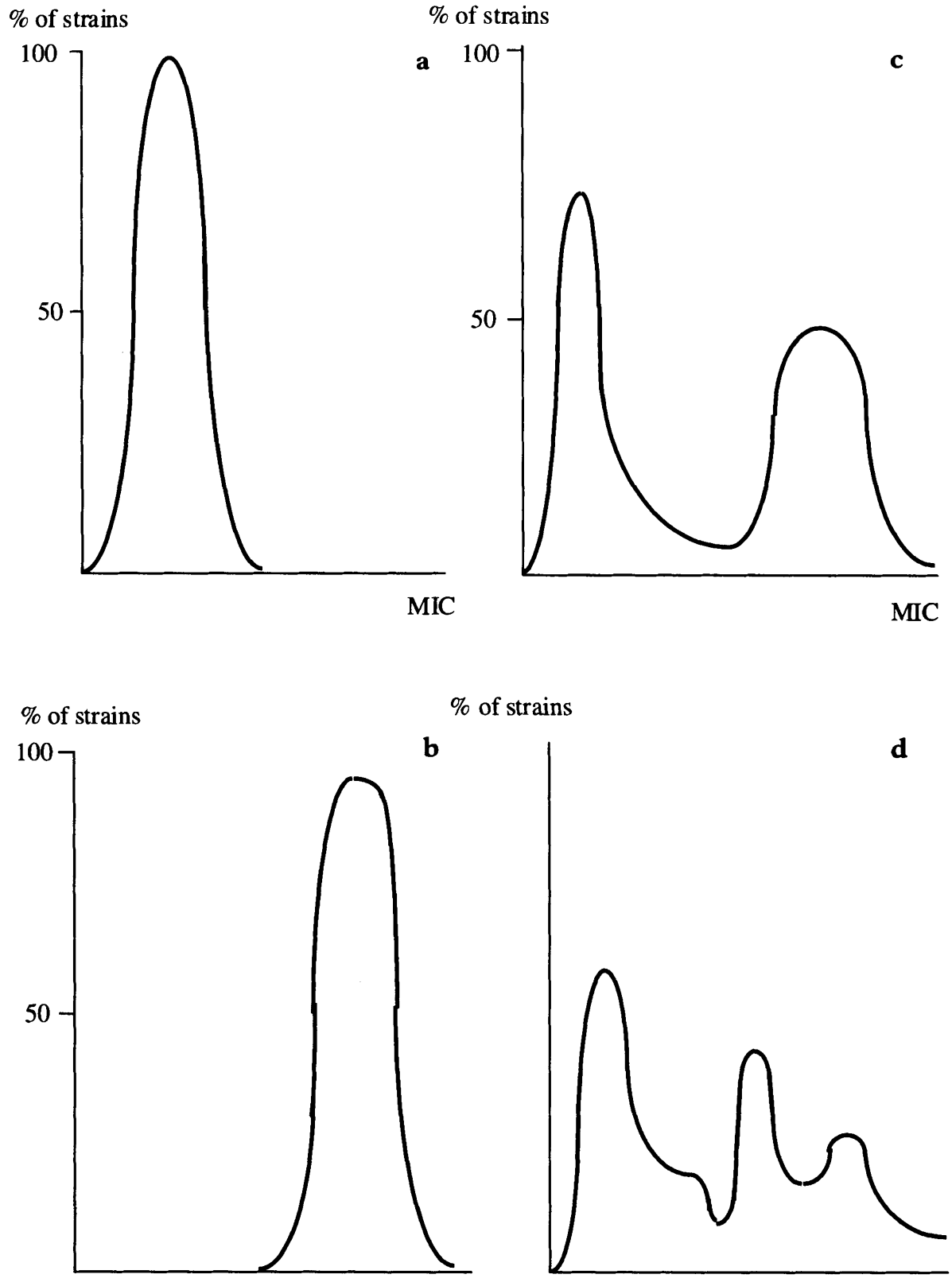

Figure 1 MIC distributions: (a, b), unimodal distribution; (c), bimodal distribution; (d), multimodal distribution.

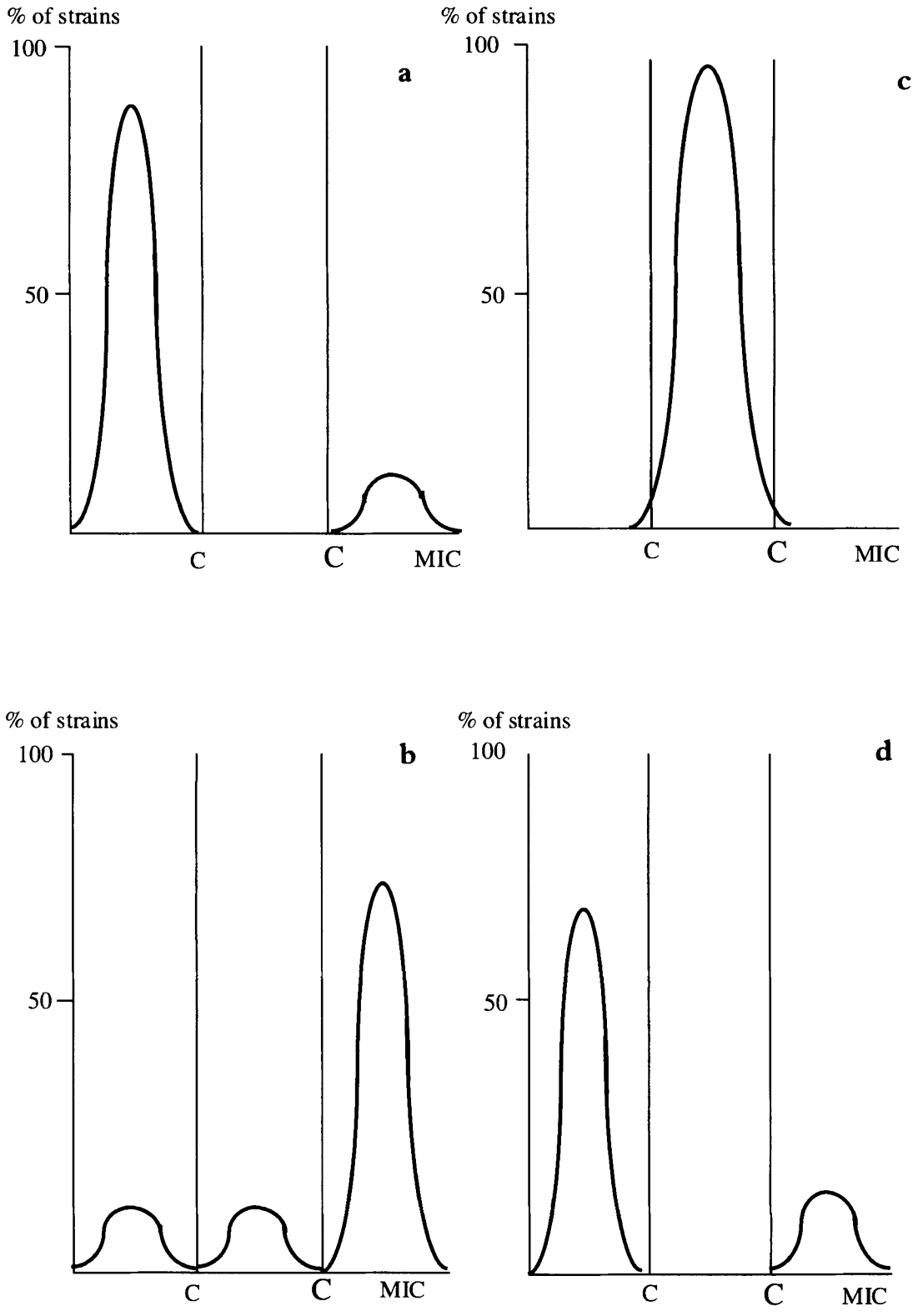

Figure 2 Classification of species in the antibacterial spectrum of activity of an antibiotic: (a), usually susceptible species; (b), resistant species; (c), moderately susceptible species; (d), non-constantly susceptible species. *c*=low breakpoint or susceptibility breakpoint; *C*=high breakpoint or resistance breakpoint.

The distribution of MICs can thus differ (Figures 1 and 2), as follows:

- Unimodal distribution: all bacteria of a species belong to a given population, i.e., susceptible or resistant.
- Bimodal distribution: there are two well individualized populations, one susceptible and the other resistant.
- Multimodal distribution: there are several populations having various levels of susceptibility.

To facilitate the classification of species, four classes have been proposed, as follows:

Usually susceptible species

These are species which are within the antibiotic's natural spectrum of activity and among which the percentage of strains with acquired resistance is low, less than 10%. The distribution of MICs is generally unimodal and below the lowest critical concentration. The physician can thus use this antibiotic at usual doses to treat an infection with a maximum safety, since the clinical trials have established the indication.

Species that are moderately susceptible or of intermediate susceptibility

These species are less susceptible to the antibiotic. This is the case with *Haemophilus influenzae* with respect to macrolides. This situation is characterized by an MIC 50% superior or equal at the low breakpoint and by an MIC 90% inferior or equal at the high breakpoint. To treat an infection caused by these bacteria, high doses of the antibiotic must be used (whenever possible) or the infection must be located in a site where the antibiotic concentrations are particularly high, greater than the MIC.

Resistant species

In this case, the MICs are distributed beyond the high critical concentration. The following situations can be distinguished:

- Species which are naturally resistant to the antibiotic and are not included in its spectrum of activity (e.g. *Staphylococcus aureus* and colistin).
- Species within the initial spectrum of activity of the antibiotic but in which the percentage of acquired resistance is high (>50%) and established with sufficient data in a country or at an international level such that this antibiotic can no longer have, outside of exceptional cases, any indication in treatment of an infection caused by a strain belonging to one of these species. This is the case with penicillin G and *Staphylococcus aureus*. However, when the in vitro test shows that the strain is susceptible, its use remains possible (for example, methicillin-resistant staphylococci are resistant to currently used fluoroquinolones in France at a rate of 80–90%; these agents, although not recommended in empirical therapy, may have a clinical indication in few documented cases).

The class where the species are listed as non-constantly susceptible

This is based on available epidemiologic information on bacterial resistance. Although the information depends on the time and location, we think that this class adjusts and updates the clinical spectrum.

It is important to call the attention of the prescriber to existing rates of resistant strains higher than 10%, so that in treating severe infections caused by a strain belonging to one of these species, the antibiotic susceptibility testing and the awareness of the physician will facilitate the decision and likely improve the outcome.

In conclusion, the antibacterial spectrum of activity of an antibiotic includes species which are initially susceptible: this is an invariable first dimension, the 'range' of the spectrum.

In addition to this initial parameter, a second related to epidemiologic changes in resistance must also be considered. The latter data must be updated regularly to take into account changes in the incidence of resistant strains within some species which have previously known mechanism of resistance and the development of new mechanisms of resistance.

Lastly, the clinician's role is to add a third dimension, which is crucial: this is the notion of clinical success or failure.

As a result of these notions, the clinical antibacterial spectrum of activity of an antibiotic provides the prescribing physician with updated information enabling him or her to choose the most suitable antibiotic to treat his or her patient.

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